sequence SEQ ID NO:12.

42. (amended) The method of claim 38 wherein the compound has the amino acid sequence SEQ ID NO:15.

A11 Cont

43. (amended) The method of claim 38 wherein the compound has the amino acid sequence SEQ ID NO:16.

A12

45. (amended) The method according to claim 44 wherein the peptide has the amino acid sequence SEQ ID NO:19 or SEQ ID NO:20.

Remarks

Claims 1-8 and 12-45 are pending in the application. The specification has been amended to assign a new sequence listing number, SEQ ID NO:22, to the amino sequence Asn-Ala-Glu-Val-Tyr. A sequence listing number was not previously assigned to that sequence. The sequence has been inserted into the sequence listing. A substitute sequence listing with the newly inserted SEQ ID NO:22 is submitted herewith.

Claim 8 has been rewritten to more distinctly point out and define the invention, and claims 9-11 have been cancelled. The amendment of claim 8 is supported by claims 12 and 13. The claims have also been amended to refer to amino acid sequences by their respective SEQ ID numbers.

The Notice to Comply states that "the specification does not set forth the corresponding SEQ ID Nos. for the recited sequences". The specification has been reviewed. The only amino acid sequence set forth in the specification which is subject to the sequence listing requirements and lacks a sequence ID number is the sequence Asn-Ala-Glu-Val-Tyr, now SEQ ID No. 22. All other sequences in the specification have assigned sequence ID numbers.

Mark-ups of the specification paragraphs and claims rewritten herein are set forth in Appendices A and B.

A

Respectfully submitted,

KEITH R. McCRAE

By: _____

DANIEL A. MONACO
Registration No. 30,480
DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
Phone: (215) 988-3312
Fax: (215) 988-2757
Attorney for the Applicant

STATEMENT UNDER 37 C.F.R. 1.825

The substitute Sequence Listing submitted herewith includes no new matter. The copy in computer readable form submitted herewith is the same as the paper copy.

Dated: July 10, 2001

_____

DANIEL A. MONACO,
RegistrationNo.30,480

APPENDIX A: Mark-up of specification paragraphs amended.

Page 6, lines 19-27:

According to another related invention, compounds of the formula X_5-Leu-Asp-X_7-SEQ ID NO:22[Asn-Ala-Glu-Val-Tyr]-X_6, wherein SEQ ID NO:22 is the sequence Asn-Ala-Glu-Val-Tyr, and pharmaceutical compositions thereof are provided wherein

X_5 is from zero to twelve amino acids, more preferably from zero to six amino acids, most preferably from zero to three amino acids;

X_6 is from zero to twelve amino acids, more preferably from zero to six amino acids, most preferably from zero to three amino acids; and

X_7 is Ala or Cys.

Where X_5 and X_6 are zero amino acids, the compounds have the sequences Leu-Asp-Cys-Asn-Ala-Glu-Val-Tyr (SEQ ID NO:21) and Leu-Asp-Ala-Asn-Ala-Glu-Val-Tyr (SEQ ID NO:12).

Page 11, lines 29-33:

"D3 peptide" means a peptide of the formula (a) X_1-SEQ ID NO:1-X_2, (b) X_3-SEQ ID NO:5-X_4, (c) X_5-Leu-Asp-X_7-SEQ ID NO:22[Asn-Ala-Glu-Val-Tyr]-X_6 were X_1, X_2, X_3, X_4, X_5, X_6 and X_7 are defined above, or (d) peptide fragment (or analog thereof) of HK domain 3 which is active in inhibiting endothelial cell proliferation and/or inhibiting angiogenesis.

APPENDIX B: Mark-up of claims amended:

1. (amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the formula X_1-[Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys]SEQ ID NO:1-X_2 wherein

X_1 is from zero to twelve amino acids, and
X_2 is from zero to twelve amino acids,

3. (amended) The composition of claim 1 wherein

X_1 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:2[Thr-Leu-Thr-His-Thr–Ile-Thr-Lys-Leu-Asn-Ala-Glu], or N-terminal truncation fragment thereof containing at least one amino acid, and

X_2 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:3[Ile-Asp-Asn-Val-Lys-Lys-Ala-Arg-Val-Gln-Val-Val], or C-terminal truncation fragment thereof containing at least one amino acid.

4. (amended) The composition of claim 1 wherein the compound has substantial amino acid sequence homology to the amino acid sequence SEQ ID NO:4[Thr-Leu-Thr-His-Thr–Ile-Thr-Lys-Leu-Asn-Ala-Glu-Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys-Ile-Asp-Asn-Val-Lys-Lys-Ala-Arg-Val-Gln-Val-Val].

5. (amended) The composition of claim 1 wherein the compound has the amino acid sequence SEQ ID NO:1[Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys].

6. (amended) The composition of claim 1 wherein the compound has the amino acid sequence SEQ ID NO:9[Thr–Ile-Thr-Lys-Leu-Asn-Ala-Glu-Asn-Asn-Ala-Thr-Phe-Tyr-Phe-

Lys].

7. (amended) The composition of claim 1 wherein the compound has the amino acid sequence SEQ ID NO:10[Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys-Ile-Asp-Asn-Val-Lys-Lys-Ala-Arg].

8. (amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the [formula X_3-Cys-Val-Gly-Cys-X_4 wherein

X_3 is from zero to twelve amino acids, and

X_4 is from zero to twelve amino acids,]

amino acid sequence SEQ ID NO:5 or SEQ ID NO:11 wherein [a] an internal disulfide bond between the cysteine residues [of the segment Cys-Val-Gly-Cys] of said compound is optionally present, and wherein said compound optionally comprises an amino-terminal and/or carboxy-terminal protecting group.

12. (amended) The composition of claim 8 wherein the compound has the amino acid sequence SEQ ID NO:5[Cys-Val-Gly-Cys].

13. (amended) The composition of claim 8 wherein the compound has the amino acid sequence SEQ ID NO:11[Thr-Lys-Ile-Cys-Val-Gly-Cys-Pro-Arg-Asp-Ile-Pro-Thr-Asn-Ser-Pro].

14. (amended) The composition of any of claims [8-13] 8, 12 or 13 wherein a disulfide bond between the cysteine residues of the [segment Cys-Val-Gly-Cys of said] compound is present.

15. (amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the formula X_5-Leu-Asp-X_7-SEQ ID NO:22[Asn-Ala-Glu-Val-Tyr]-X_6 wherein

X_5 is from zero to twelve amino acids,

X_6 is from zero to twelve amino acids, and

X_7 is Ala or Cys,

and wherein said compound optionally comprises an amino-terminal and/or carboxy-terminal protecting group.

17. (amended) The composition of claim 15 wherein

X_5 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:13[Thr-Glu-Ser-Cys-Glu-Thr-Lys-Lys-Leu-Gly-Gln-Ser], or N-terminal truncation fragment thereof containing at least one amino acid, and

X_6 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:14[Val-Val-Pro-Trp-Glu-Lys-Lys-Ile-Tyr-Pro-Thr-Val], or C-terminal truncation fragment thereof containing at least one amino acid.

18. (amended) The composition of claim 15 wherein the compound has substantial amino acid sequence homology to the amino acid sequence SEQ ID NO:17[Thr-Glu-Ser-Cys-Glu-Thr-Lys-Lys-Leu-Gly-Gln-Ser-Leu-Asp-Ala-Asn-Ala-Glu-Val-Tyr-Val-Val-Pro-Trp-Glu-Lys-Lys-Ile-Tyr-Pro-Thr-Val].

19. (amended) The composition of claim 15 wherein the compound has the amino acid sequence SEQ ID NO:12[Leu-Asp-Ala-Asn-Ala-Glu-Val-Tyr].

20. (amended) The composition of claim 15 wherein the compound has the amino acid sequence SEQ ID NO:15[Glu-Thr-Lys-Lys-Leu-Gly-Gln-Ser-Leu-Asp-Ala-Asn-Ala-Glu-Val-Tyr].

21. (amended) The composition of claim 15 wherein the compound has the amino acid sequence SEQ ID NO:16[Leu-Asp-Ala-Asn-Ala-Glu-Val-Tyr-Val-Val-Pro-Trp-Glu-Lys-

Lys-Ile].

23. (amended) The composition according to claim 22 wherein the peptide fragment or analog has the amino acid sequence SEQ ID NO:19[Tyr-Phe-Ile-Asp-Phe-Val-Ala-Arg-Glu-Thr-Thr-Cys-Ser-Lys-Glu-Ser] or SEQ ID NO:20[Tyr-Phe-Ile-Asp-Phe-Val-Ala-Arg-Glu-Thr-Thr-Ala-Ser-Lys-Glu-Ser].

27. (amended) A method of inhibiting endothelial cell proliferation comprising contacting endothelial cells with a compound of the formula X_1-SEQ ID NO:1[Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys]-X_2 wherein

X_1 is from zero to twelve amino acids, and
X_2 is from zero to twelve amino acids,

and wherein said compound optionally comprises an amino-terminal and/or carboxy-terminal protecting group.

29. (amended) The method of claim 27 wherein

X_1 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:2[Thr-Leu-Thr-His-Thr–Ile-Thr-Lys-Leu-Asn-Ala-Glu], or N-terminal truncation fragment thereof containing at least one amino acid, and

X_2 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:3[Ile-Asp-Asn-Val-Lys-Lys-Ala-Arg-Val-Gln-Val-Val], or C-terminal truncation fragment thereof containing at least one amino acid.

30. (amended) The method of claim 27 wherein the compound has the amino acid

sequence SEQ ID NO:9[Thr–Ile-Thr-Lys-Leu-Asn-Ala-Glu-Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys].

31. (amended) The method of claim 27 wherein the compound has the amino acid sequence SEQ ID NO:10[Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys-Ile-Asp-Asn-Val-Lys-Lys-Ala-Arg].

32. (amended) A method of inhibiting endothelial cell proliferation comprising contacting endothelial cells with a compound of the formula X_3-SEQ ID NO:5[Cys-Val-Gly-Cys]-X_4 wherein

X_3 is from zero to twelve amino acids, and
X_4 is from zero to twelve amino acids,

wherein a disulfide bond between the cysteine residues of the segment SEQ ID NO:5[Cys-Val-Gly-Cys] is optionally present, and wherein said compound optionally comprises an amino-terminal and/or carboxy-terminal protecting group.

34. (amended) The method of claim 32 wherein

X_3 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:6[Gly-Lys-Asp-Phe-Val-Gln-Pro-Pro-Thr-Lys-Ile], or N-terminal truncation fragment thereof containing at least one amino acid, and

X_4 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:7[Pro-Arg-Asp-Ile-Pro-Thr-Asn-Ser-Pro-Glu-Leu-Glu], or C-terminal truncation fragment thereof containing at least one amino acid.

35. (amended) The method of claim 32 wherein the compound has the amino acid sequence SEQ ID NO:5[Cys-Val-Gly-Cys].

36. (amended) The method of claim 32 wherein the compound has the amino acid sequence SEQ ID NO:11[Thr-Lys-Ile-Cys-Val-Gly-Cys-Pro-Arg-Asp-Ile-Pro-Thr-Asn-Ser-Pro].

37. (amended) The method of any of claims 32-36 wherein a disulfide bond between the cysteine residues of the segment SEQ ID NO:5[Cys-Val-Gly-Cys] of said compound is present.

38. (amended) A method of inhibiting endothelial cell proliferation comprising contacting endothelial cells with a compound of the formula X_5-Leu-Asp-X_7-SEQ ID NO:22[Asn-Ala-Glu-Val-Tyr]-X_6 wherein

X_5 is from zero to twelve amino acids,
X_6 is from zero to twelve amino acids, and
X_7 is Ala or Cys.

and wherein said compound optionally comprises an amino-terminal and/or carboxy-terminal protecting group.

40. (amended) The method of claim 38 wherein

X_5 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:13[Thr-Glu-Ser-Cys-Glu-Thr-Lys-Lys-Leu-Gly-Gln-Ser], or N-terminal truncation fragment thereof containing at least one amino acid, and

X_6 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:14[Val-Val-Pro-Trp-Glu-Lys-Lys-Ile-Tyr-

Pro-Thr-Val], or C-terminal truncation fragment thereof containing at least one amino acid.

41. (amended) The method of claim 38 wherein the compound has the amino acid sequence SEQ ID NO:12[Leu-Asp-Ala-Asn-Ala-Glu-Val-Tyr].

42. The method of claim 38 wherein the compound has the amino acid sequence SEQ ID NO:15[Glu-Thr-Lys-Lys-Leu-Gly-Gln-Ser-Leu-Asp-Ala-Asn-Ala-Glu-Val-Tyr].

43. (amended) The method of claim 38 wherein the compound has the amino acid sequence SEQ ID NO:16[Leu-Asp-Ala-Asn-Ala-Glu-Val-Tyr-Val-Val-Pro-Trp-Glu-Lys-Lys-Ile].

45. (amended) The method according to claim 44 wherein the peptide has the amino acid sequence SEQ ID NO:19[Tyr-Phe-Ile-Asp-Phe-Val-Ala-Arg-Glu-Thr-Thr-Cys-Ser-Lys-Glu-Ser] or SEQ ID NO:20[Tyr-Phe-Ile-Asp-Phe-Val-Ala-Arg-Glu-Thr-Thr-Ala-Ser-Lys-Glu-Ser].